Synthetic peptides homologous to prion protein residues 106-147 form amyloid-like fibrils in vitro.

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Abstract

Gerstmann-Sträussler-Scheinker disease (GSS) is a prion-related encephalopathy pathologically characterized by massive deposition of prion protein (PrP) amyloid in the central nervous system. The major component of amyloid fibrils isolated from patients of the Indiana kindred of GSS (GSS-Ik) is an 11-kDa fragment of PrP spanning residues 58 to approximately 150. These patients carry a missense mutation of the PRNP gene, causing a Phe-->Ser substitution at codon 198. We investigated fibrillogenesis in vitro by using synthetic peptides homologous to consecutive segments of GSS-Ik amyloid protein (residues 57-64, 89-106, 106-126, and 127-147) as well as peptides from the PrP region with the GSS-Ik mutation (residues 191-205 and 181-205, both wild type and mutant). Peptide PrP-(106-126) formed straight fibrils similar to those extracted from GSS brains, whereas peptide PrP-(127-147) formed twisted fibrils resembling scrapie-associated fibrils isolated from subjects with transmissible spongiform encephalopathies. Congo red staining and x-ray fibril diffraction showed that both straight and twisted fibrils had tinctorial and conformational properties of native amyloid. Conversely, the other peptides did not form amyloid-like fibrils under similar conditions. These findings suggest that the sequence spanning residues 106-147 of PrP is central to amyloid fibril formation in GSS and related encephalopathies.

MeSH

Amino Acid Sequence; Amyloid; Amyloid Neuropathies; Crystallography, X-Ray; Human; In Vitro; Microscopy, Electron; Molecular Sequence Data; Nerve Tissue Proteins; Peptides; Polymers; PrPSc Proteins; Prions; Solubility; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

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Lawrence, D. A. Goldman, and R. T. Hood, Bull Math Biol. 48, 569 (1986)], three of these are only apparent at low threshold settings for standard deviation. The strongest identity is between sequences at the carboxyl ends of the NBFs. Of the 66 residues aligned 27% are identical and another 11% are functionally similar. The overall weak internal homology is in contrast to the much higher degree (>70%) in P-glycoprotein for which a gene duplication hypothesis has been proposed (Gros et al, Cell 47, 371, 1986, C. Chen et al, Cell 47, 381, 1986, Gerlach et al, Nature, 324, 485, 1986, Gros et al, Mol. Cell. Biol. 8, 2770, 1988). The lack of conservation in the relative positions of the exon-intron boundaries may argue against such a model for CFTR (Figure 2).

Since there is apparently no signal-peptide sequence at the amino-terminus of CFTR, the highly charged hydrophilic segment preceding the first transmembrane sequence is probably oriented in the cytoplasm. Each of the 2 sets of hydrophobic helices are expected to form 3 transversing loops across the membrane and little sequence of the entire protein is expected to be exposed to the exterior surface, except the region between transmembrane segment 7 and 8. It is of interest to note that the latter region contains two potential sites for N-linked glycosylation.

Each of the membrane-associated regions is followed by a NBF as indicated above. In addition, a highly charged cytoplasmic domain can be identified in the middle of the predicted CFTR polypeptide, linking the 2 halves of the protein. This domain, named the R-domain, is operationally defined by a single large exon in which 69 of the 241 amino acids are polar residues arranged in alternating clusters of positive and negative charges. Moreover, 9 of the 10 consensus sequences required for phosphosphorylation by protein kinase A (PKA), and, 7 of the potential substrate sites for protein kinase C (PKC) found in CFTR are located in this exon.